

Short Note

(E)-1-(2-Aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one

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Abstract: The title chalcone (E)-1-(2-aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one was prepared with an excellent yield from a Claisen–Schmidt condensation reaction between *o*-aminoacetophenone and *p*-chlorobenzaldehyde. This product will be used as a key precursor for the development of an alternative route for the total synthesis of dubamine and graveoline alkaloids. Single crystals of the title compound suitable for X-ray diffraction were grown via slow evaporation in ethanol at room temperature. A complete crystallographic study was performed in depth to unequivocally confirm its structure and determine some interesting supramolecular properties. The crystal structure of the title *o*-aminochalcone, C₁₅H₁₂ClNO, shows two molecules per asymmetric unit (*Z'* = 2) and adopts an *E* configuration about the C=C double bond. In the title compound, the mean plane of the non-H atoms of the central chalcone fragment C—C(O)—C—C is as follows: [r.m.s. deviation = 0.0130 Å for A-B and 0.0043 for C-D molecules]. In the crystal, molecules are linked by N—H...N and C—H...O, hydrogen bonds forming edge-fused R⁶₆(46) rings parallel to (100). Additionally, N—H...O hydrogen bonds generate a three-dimensional network.

Keywords: *o*-aminoacetophenones; Claisen–Schmidt condensation; *o*-aminochalcones; single crystal X-ray diffraction

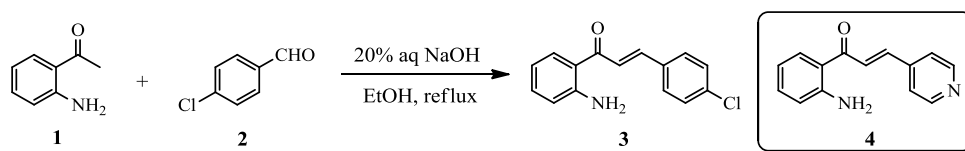
1. Introduction

Chalcones are synthetic or naturally occurring α,β -unsaturated diaryl ketones which have shown a wide spectrum of biological activities as anti-tubercular [1], anti-inflammatory [2], antimalarial [3], antibacterial [4], antifungal [5], and mainly antitumor agents [6]. These compounds have also been widely used as precursors for diverse synthetic approaches, mainly in the synthesis of heterocyclic compounds [7,8]. In this sense, and continuing with our current studies on the synthetic utility of *o*-aminochalcones [9,10], the amino-derivative **3**, and analogues, were obtained from the condensation reaction of *o*-aminoacetophenone **1** and *p*-chlorobenzaldehyde **2** (Scheme 1) to be subsequently transformed into heterocyclic alkaloids of biological interest.

2. Results and Discussion

Currently, our studies are focused in developing an alternative straightforward approach for the total synthesis of dubamine and graveoline alkaloids starting from a common quinolone precursor. For that, *o*-aminochalcones were visualized as key precursors for our goals. In consequence, several of them were synthesized including the target compound **3**. This product was obtained with an

excellent yield from equimolar amounts of *o*-aminoacetophenone **1** and *p*-chlorobenzaldehyde **2** via a Claisen–Schmidt condensation reaction as shown in Scheme 1. Reaction proceeded in ethanol at reflux and catalyzed by NaOH. The starting materials were consumed after 20 min of heating (TLC control), and the residue was crystallized from ethanol, affording a yellow solid. After analysis by analytical and spectroscopic techniques, the formation of the expected chalcone **3** with a 97% yield was confirmed. During purification, we noticed that pale yellow crystals formed from the ethanolic mother liquor.



Scheme 1. Synthesis of *o*-aminochalcone **3**. Structure **4** will be used below to compare some of its crystallographic properties with those of compound **3**.

It is worth mentioning that *o*-aminochalcone **3** has previously been reported [11] and is currently a commercially available product [12]. Lee and Youn prepared it from a condensation reaction between ketone **1** and aldehyde **2** in a THF–NaOMe mixture. After a laborious workup, compound **3** was obtained with an 82% yield; however, no details about its characterization were supplied [11]. In spite of compound **3** being a known molecule, no crystallographic analysis has been reported. This finding encouraged us to collect and select the best crystals and solve the structure via X-ray diffraction. Before starting the X-ray analysis, we considered that a complete analytical and spectroscopic characterization of compound **3** would be worthwhile. IR, 1D and 2D NMR techniques, and mass spectrum and elemental analysis were used. The most relevant spectroscopic features for compound **3** are the NH₂ and C=O absorption bands at (3468, 3321) and 1643 cm^{−1}, respectively, in the IR spectrum. In the ¹H-NMR spectrum, two doublets at 7.59 (*J* = 15.5 Hz, 1H) and 7.99 (*J* = 15.5 Hz, 1H) ppm, assigned to the α,β-vinyl protons in *trans* configuration associated with the new C=C bond, formed. A broad singlet at 7.42 ppm (2H) was assigned to the NH₂ functionality.

The ¹³C-NMR signals for all 13 different C nuclei expected for **3** were observed, one of which belongs to the carbonyl group at 190.8 ppm. Two molecular ions with *m/z* 257/259 (accomplishing the Cl-rule), and a base peak with *m/z* 146 (*M* – C₆H₄Cl), are consistent with the proposed structure for chalcone **3**.

2.1. Structural Analysis

Single crystals of **3** suitable for X-ray diffraction were grown via slow evaporation in ethanol at room temperature. According to the results (Figures 1–3 and Tables 1 and 2), there is no doubt that the obtained compound corresponded to chalcone **3** as proposed above in the Scheme 1.

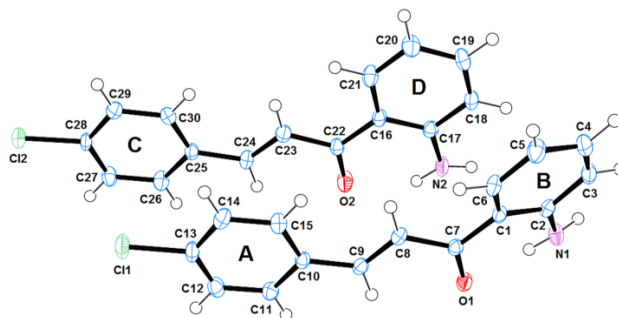


Figure 1. ORTEP drawing of the asymmetric unit for the *o*-aminochalcone **3**; ellipsoids are displayed at the 50% probability level.

Table 1. Selected bond lengths [Å], angles [°] and torsion angles [°] for chalcone **3**.

Bond Lengths	
Cl(1)-C(13); 1.7391(18)	C(2)-N(1); 1.372(3)
Cl(2)-C(28); 1.7401(18)	C(16)-C(22); 1.467(3)
C(7)-C(8); 1.482(2)	C(22)-C(23); 1.483(3)
C(8)-C(9); 1.332(3)	C(23)-C(24); 1.325(3)
C(9)-C(10); 1.468(2)	C(24)-C(25); 1.468(2)
C(7)-O(1); 1.238(2)	C(17)-N(2); 1.353(3)
C(1)-C(7); 1.472(3)	
Angles	
C(7)-C(8)-C(9); 120.15(18)	C(22)-C(23)-C(24); 120.65(19)
Torsion angles	
C(2)-C(1)-C(7)-O(1); 22.9(3)	C(17)-C(16)-C(22)-O(2); 0.8(3)
C(8)-C(7)-C(1)-C(2); -154.66(17)	C(23)-C(22)-C(16)-C(17); -178.05(17)
C(10)-C(9)-C(8)-C(7); -177.55(17)	C(25)-C(24)-C(23)-C(22); -179.20(19)

In the title chalcone **3**, marked structural differences in the molecules of the asymmetric unit are observed. Central fragments C1/C7(O1)/C8/C9/C10 and C16/C22(O2)/C23/C24/C25 are almost planar with an r.m.s. deviation of 0.0043 Å and 0.0130 Å, respectively. The C1/C7(O1)/C8/C9/C10 fragment makes dihedral angles of 26.14(12)° and 5.73(19)°, with A and B rings, respectively. At the same time, the C16/C22(O2)/C23/C24/C25 fragment makes dihedral angles of 1.97(18)° and 4.72(16)°, with C and D rings, respectively (see Figure 1). The amino groups are *syn* positioned with respect to the carbonyl groups in both molecules.

Bond lengths and bond angles in **3** are in a good agreement with those of the common fragments of the recently reported and closely related *o*-aminochalcone **4** [13], Scheme 1. The reported structure for **4** bears a close similarity to that of the title compound **3** including the internal NH...O hydrogen bond, with the exception of the values in the bond length of the double bonds C8–C9 and C23–C24. In the title *o*-aminochalcone **3**, these bond lengths are 1.332(3) and 1.325(3) Å, whereas they appear as a unique value of 1.299(3) Å in **4**.

2.2. Supramolecular Features

The packing arrangement of the title *o*-aminochalcone **3** can be described by N–H...O and N–H...N hydrogen bonds of medium-strength and weak C–H...O intermolecular contacts. The N–H...N and C–H...O interactions are responsible for crystal growth parallel to the direction [100]. In these interactions, the N2–H4N in the molecule at (x,y,z) acts as a hydrogen-bond donor to the N1 atom of the amino group at (x-1/2,-y+1/2,-z+2). Interactions on this plane are complemented by donors of hydrogen bonding: C14–H and C29–H in the molecule at (x,y,z) to carbonyl O2 and O1 atoms at (-x+1,+y-1/2,-z+3/2) (see Figure 2 and Table 2). These interactions generate a chain of edge-fused R₆⁶(46) rings growing parallel to the plane [100]. Moreover, an intramolecular S(6) ring that helps to stabilize the structure is observed.

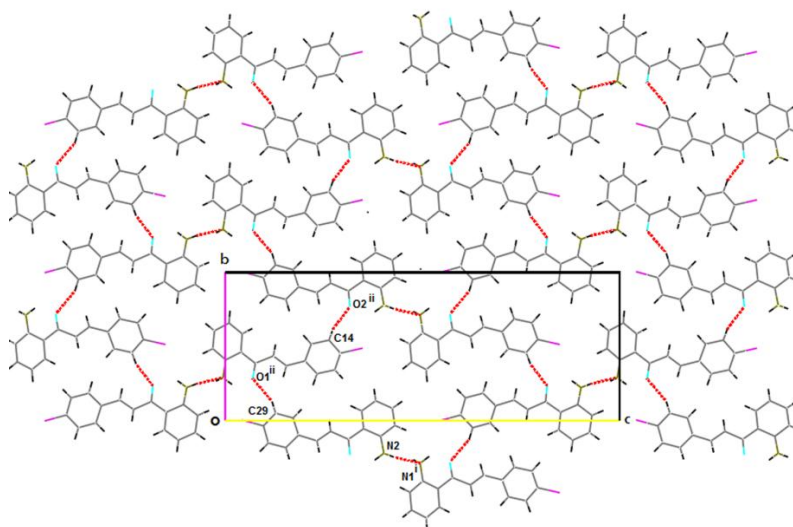


Figure 2. Partial packing diagram showing the two-dimensional sheet network of molecules in the *bc* plane, the formation of which is governed by the occurrence of N–H...N and C–H...O hydrogen bonds, forming edge-fused $R^6_6(46)$ rings parallel to the direction [100]. Hydrogen bonds are depicted with dashed lines. (Symmetry codes: (i) $x-1/2, -y+1/2, -z+2$; (ii) $-x+1, y-1/2, -z+3/2$).

Table 2. Hydrogen bond lengths [Å] and angles [°] for chalcone **3**.

D–H...A	D–H	H...A	D...A	D–H...A
N1–H2N...O1 ⁱ	0.89(3)	2.09(4)	2.982(3)	176(3)
N2–H4N...N1 ⁱ	0.83(3)	2.48(3)	3.269(3)	158(2)
C14–H14...O2 ⁱⁱ	0.95	2.40	3.293(3)	157.3
C29–H29...O1 ⁱⁱ	0.95	2.53	3.400(3)	152.7
N2–H3N...O2	0.89(3)	1.95(3)	2.633(3)	133(3)
N1–H1N...O1	0.88(3)	2.08(3)	2.699(3)	127(3)

Symmetry codes: (i) $x-1/2, -y+1/2, -z+2$; (ii) $-x+1, y-1/2, -z+3/2$.

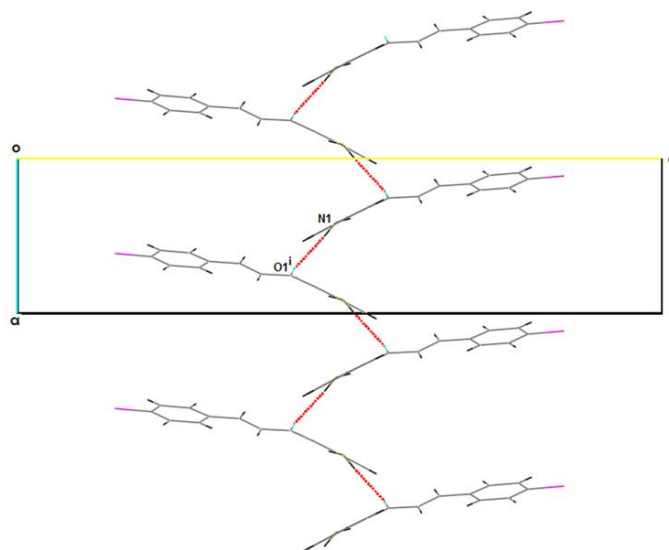


Figure 3. Part of the crystal structure of **3**, showing the formation of C(6) chains along the direction [100]. (Symmetry code: (i) $x-1/2, -y+1/2, -z+2$).

Other N–H...O hydrogen bonds are further observed that run along the direction [100] (see Figure 3). The N1–H2N of the amino group in the first molecule of **3** at (x,y,z) acts as hydrogen bond donor to carbonyl O1 atom of the second molecule at (x-1/2,-y+1/2,-z+2). Finally, the O1 atom in the first molecule promotes simultaneous interactions with N1 and C29 in different directions, which is not noted for its counterpart (i.e. the O2 atom of the carbonyl group) in the second molecule. The rotation of the **A** ring relative to the central segment of the chalcone brings the O1 atom to other hydrogen bond donors, including the N1–H2N along the direction [100].

3. Materials and Methods

3.1. General Information

Melting point was determined on a Büchi melting point B-450 apparatus (Instrumart, South Burlington, VT, USA) and is uncorrected. IR spectra were recorded on a Shimadzu FTIR 8400 spectrophotometer (Scientific Instruments Inc., Seattle, WA, USA) using KBr disks. ¹H and ¹³C-NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) operating at 400 MHz and 100 MHz, respectively, and using CDCl₃ as a solvent and tetramethylsilane as an internal standard. The mass spectrum was obtained on a SHIMADZU-GCMS 2010-DI-2010 spectrometer (Scientific Instruments Inc., Columbia, NC, USA), equipped with a direct inlet probe) operating at 70 eV. Microanalysis was performed on a Thermo-Finnigan Flash EA1112 CHN elemental analyzer (Thermo Fischer Scientific Inc., Madison, WI, USA), and the values are within ±0.4% of the theoretical values. Silica gel aluminum plates (Merck 60 F₂₅₄) were used for analytical TLC. The starting ketone **1** and aldehyde **2** were purchased from (Sigma-Aldrich, San Luis, MO, USA) analytical or reagent grades and were used without further purification.

3.2. Synthesis of (E)-1-(2-Aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**3**)

A mixture of *o*-aminoacetophenone **1** (0.5 g, 1 mmol), *p*-chlorobenzaldehyde **2** (1 mmol), a 20% NaOH aqueous solution (0.5 mL), and 96% EtOH (5 mL) was subjected to reflux for 20 min. The solid formed was filtered and washed with ethanol and water (10:5 mL). Recrystallization from 96% ethanol afforded **3** (97% yield, yellow solid, m.p. 94–95 °C). FTIR (KBr): ν = 3468, 3321 (NH₂), 3034, 2974, 1643 (C=O), 1610, 1570, 1207, 1155, 750 str cm⁻¹. ¹H-NMR (400 MHz, DMSO-*d*₆) δ : 6.59 (t, *J* = 8.2, 1H, H-4), 6.80 (d, *J* = 8.2 Hz, 1H, H-3), 7.28 (t, *J* = 8.2, 1H, H-5), 7.42 (bs, 2H, NH₂), 7.48 (d, *J* = 8.4, 2H, H-11,14), 7.59 (d, *J* = 15.5 Hz, 1H, H-9), 7.87 (d, *J* = 8.4 Hz, 2H, H-11,15), 7.99 (d, *J* = 15.5 Hz, 1H, H-8), 8.07 (d, *J* = 8.2 Hz, 1H, H-6) ppm. ¹³C-NMR (100 MHz, DMSO-*d*₆) δ : 114.9 (C-4), 117.4 (C-3), 117.9 (C-2), 124.7 (C-8), 129.4 (C-12,14), 130.8 (C-11,15), 131.9 (C-6), 134.5 (C-10), 134.9 (C-5), 135.0 (C-13), 140.9 (C-9), 152.6 (C-1), 190.8 (C-7, C=O) ppm. The numbering of the C and H atoms is the same than that for the structure **3** in Figure 1. Anal. calcd. for C₁₅H₁₂ClNO (257.06): C, 69.91; H, 4.69; N, 5.43. Found: C, 70.05; H, 4.58; N, 5.52. MS (EI, 70 eV) *m/z* (%): 257/259 (20.4/6.8) [M⁺], 256 (31), 146 (100).

Crystal Data: C₁₅H₁₂ClNO (*M* = 257.71 g/mol): orthorhombic, space group P2₁2₁2₁ (no. 19), *a* = 7.2156(2) Å, *b* = 11.2733(3) Å, *c* = 30.0334(7) Å, *V* = 2443.03(11) Å³, *Z* = 8, *T* = 123(2) K, μ (MoK α) = 0.298 mm⁻¹, *D*_{calc} = 1.401 Mg/m³, 12065 reflections measured (3.267° ≤ Θ ≤ 28.87°), 5488 unique (*R*_{int} = 0.0255, *R*_{sigma} = 0.0401) which were used in all calculations. The final *R*1 was 0.0379 (*I* > 2 σ (*I*)) and *wR*2 was 0.0782 (all data).

Data Collection and Refinement Details: Diffraction data was collected on an Oxford Diffraction Xcalibur E diffractometer using graphite monochromated MoK α radiation (0.71073 Å). The corrected data was solved by direct methods with SHELXS-97 and refined by full-matrix methods on F² with SHELXL-2014 [14]. All H-atoms, except for H–N, were positioned at geometrically idealized positions, C–H = 0.9500 Å, and were refined using a riding model approximation with *U*_{iso}(H) = 1.2 *U*_{eq}(parent atom). H–N atoms were found from the Fourier difference maps, and their coordinates were freely

refined. Correctness of the model was confirmed by low residual peaks (0.246) and holes ($-0.255 \text{ e.}\text{\AA}^{-3}$) in the final difference map. (CCDC 1501017 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk)).

Supplementary Materials: Copies of the IR, ^1H -, ^{13}C -NMR, DEPT-135, 2D NMR and mass spectra and the checkCIF and CIF files for compound **3** can be found at <http://www.mdpi.com/1422-8599/2016/4/M911>.

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Author Contributions: R.A. designed the experiments; L.C. performed the experiments; R.A., L.C., J.Q., and B.I. analyzed the IR, MS, and NMR spectral data and wrote the manuscript; R.M-F. and A.R.K. performed the measurement and analysis of the X-ray experiments and helped to write the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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